8-319

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Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: MICHAEL BARKER Examiner # : 81519 Date: 8.8.06

Art Unit: 1626 Phone Number: 2-4341 Serial Number: 10/500,888

REM Location (Bldg/Room#): 5C19 (Mailbox #): 5C18 Results Format Preferred (circle): (PAPER) DISK

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: Resistance-repellent retroviral protease inhibitors

Inventors (please provide full names): John W. Erickson; Michael Eisenstat; Abelardo Silva; Sergei Gulnik

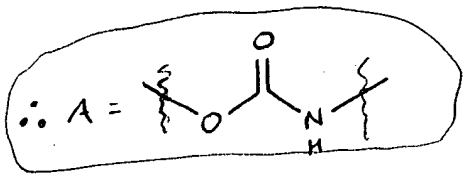
Earliest Priority Date: 5.29.02

Search Topic:

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Search:

Claim 1 wherein A = ZCZNH and Z = O ∴ A = 

X-A-B-A'-X'

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Display History

Michael Barker 10/500,888

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=> d his l1-l2;d que stat l2; d que stat l6;  d que stat l9; d his ful l10-

     FILE 'REGISTRY' ENTERED AT 13:16:06 ON 10 AUG 2006
                ACT BARKER/A
                ---------
L1               STR
L2          2161 SEA FILE=REGISTRY SSS FUL L1


L1               STR

          11      12  13      14
          O       G2  OH      G2                  C==O
          ||      /   /       /                  @15 16
Hy~O~C==NH~C~C~C~N~G1~Cy
 1  2   3   4   5   6   7   8   9   10

VAR G1=15/SO2
VAR G2=CB/AK
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT   IS SAT  AT   1
GGCAT   IS UNS  AT  10
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  16

STEREO ATTRIBUTES: NONE
L2          2161 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED   32192 ITERATIONS                      2161 ANSWERS
SEARCH TIME: 00.00.01



L3               STR

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          ||      /   /       /                  @15 16
Hy~O~C==NH~C~C~C~N~G1~Cy
 1  2   3   4   5   6   7   8   9   10

VAR G1=15/SO2
VAR G2=CB/AK
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT   IS SAT  AT   1
GGCAT   IS UNS  AT  10
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
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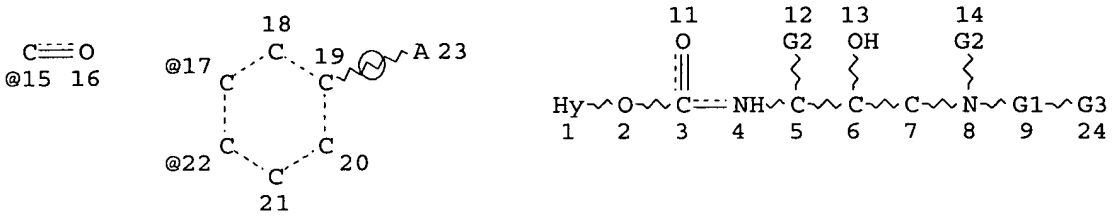
L5 STR



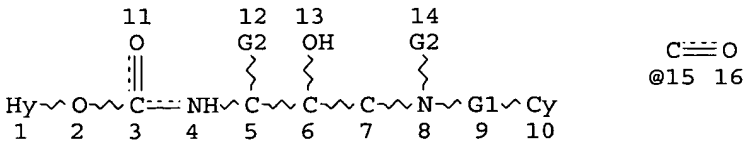
VAR G1=15/SO2
VAR G2=CB/AK
VAR G3=22/17
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS SAT AT 1
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 23

STEREO ATTRIBUTES: NONE
L6 1081 SEA FILE=REGISTRY SUB=L4 SSS FUL L5

100.0% PROCESSED 2161 ITERATIONS 1081 ANSWERS
SEARCH TIME: 00.00.01

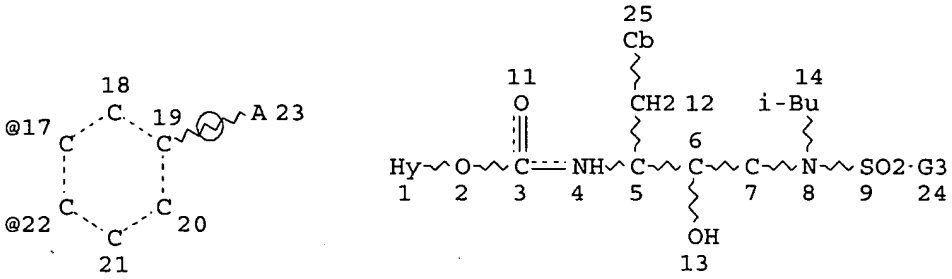
L1 STR



VAR G1=15/SO2
VAR G2=CB/AK
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS SAT AT 1
GGCAT IS UNS AT 10
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
L2 2161 SEA FILE=REGISTRY SSS FUL L1
L7 STR



VAR G3=22/17
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS SAT AT 1
GGCAT IS MCY UNS AT 25
DEFAULT ECLEVEL IS LIMITED

narrower search

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L9 691 SEA FILE=REGISTRY SUB=L2 SSS FUL L7

100.0% PROCESSED 2161 ITERATIONS 691 ANSWERS
SEARCH TIME: 00.00.01

FILE 'CAPLUS' ENTERED AT 13:18:52 ON 10 AUG 2006
L10 935 SEA ABB=ON PLU=ON L2
L11 36 SEA ABB=ON PLU=ON L6
L12 29 SEA ABB=ON PLU=ON L9
L13 770239 SEA ABB=ON PLU=ON REPELLENT?/OBI OR RESISTANT/OBI OR RESISTANCE/OBI
L14 14 SEA ABB=ON PLU=ON L11 AND L13
L15 283 SEA ABB=ON PLU=ON L10 AND L13
L16 276 SEA ABB=ON PLU=ON L15 AND (1 OR 63)/SC,SX
SELECT RN L14 1-14 HIT
E ERICKSON J?/AU
L17 926 SEA ABB=ON PLU=ON ERICKSON J?/AU
L18 43 SEA ABB=ON PLU=ON EISSENSTAT M?/AU
L19 1437 SEA ABB=ON PLU=ON SILVA A?/AU
L20 57 SEA ABB=ON PLU=ON GULNIK S?/AU
L21 2387 SEA ABB=ON PLU=ON (L17 OR L18 OR L19 OR L20)
L22 11 SEA ABB=ON PLU=ON L21 AND L10

=> fil reg
FILE 'REGISTRY' ENTERED AT 13:31:05 ON 10 AUG 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 9 AUG 2006 HIGHEST RN 900096-56-2
DICTIONARY FILE UPDATES: 9 AUG 2006 HIGHEST RN 900096-56-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

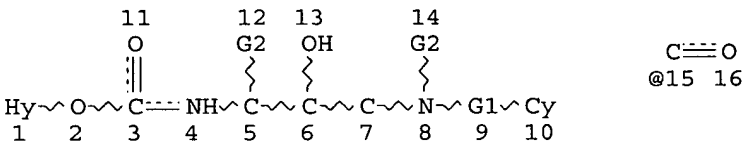
TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> d que sta l2
L1 STR



VAR G1=15/SO2
VAR G2=CB/AK
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS SAT AT 1
GGCAT IS UNS AT 10
DEFAULT ECLEVEL IS LIMITED

broad search

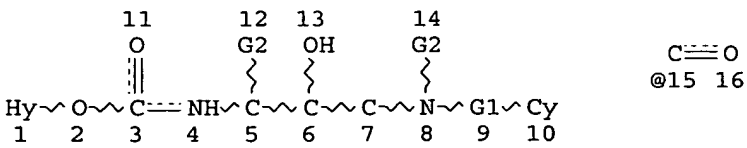
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
L2 2161 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 32192 ITERATIONS 2161 ANSWERS
SEARCH TIME: 00.00.01

=> d que stat l6
L3 STR

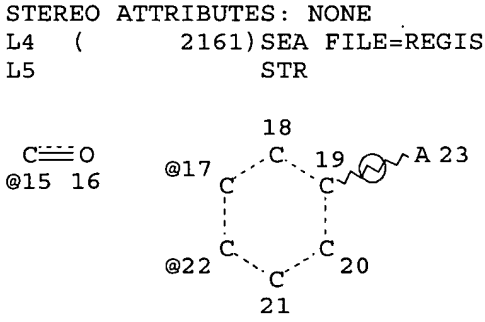
narrowed search

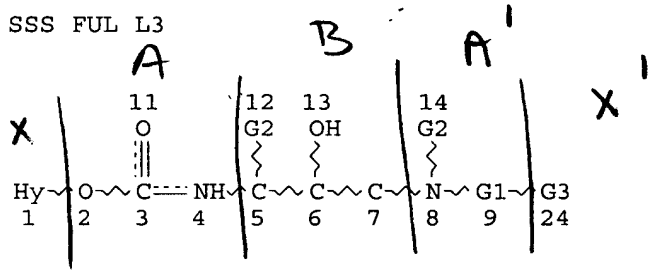


VAR G1=15/SO2
VAR G2=CB/AK
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS SAT AT 1
GGCAT IS UNS AT 10
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 16

STEREO ATTRIBUTES: NONE
L4 (2161) SEA FILE=REGISTRY SSS FUL L3
L5 STR





Narrowed Search

VAR G1=15/SO2
VAR G2=CB/AK
VAR G3=22/17
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT IS SAT AT 1
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 23

STEREO ATTRIBUTES: NONE
L6 1081 SEA FILE=REGISTRY SUB=L4 SSS FUL L5

100.0% PROCESSED 2161 ITERATIONS 1081 ANSWERS
SEARCH TIME: 00.00.01

=> fil caplus
FILE 'CAPLUS' ENTERED AT 13:31:23 ON 10 AUG 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 10 Aug 2006 VOL 145 ISS 7
FILE LAST UPDATED: 9 Aug 2006 (20060809/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

=> d que nos l14

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L3              STR
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L5              STR
L6          1081 SEA FILE=REGISTRY SUB=L4 SSS FUL L5
L11           36 SEA FILE=CAPLUS ABB=ON  PLU=ON  L6
L13       770239 SEA FILE=CAPLUS ABB=ON  PLU=ON  REPELLENT?/OBI OR  RESISTANT/OB
                 I OR RESISTANCE/OBI
L14           14 SEA FILE=CAPLUS ABB=ON  PLU=ON  L11 AND L13
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=> d que nos l22

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L1              STR
L2          2161 SEA FILE=REGISTRY SSS FUL L1
L10          935 SEA FILE=CAPLUS ABB=ON  PLU=ON  L2
L17          926 SEA FILE=CAPLUS ABB=ON  PLU=ON  ERICKSON J?/AU
L18           43 SEA FILE=CAPLUS ABB=ON  PLU=ON  EISSENSTAT M?/AU
L19         1437 SEA FILE=CAPLUS ABB=ON  PLU=ON  SILVA A?/AU
L20           57 SEA FILE=CAPLUS ABB=ON  PLU=ON  GULNIK S?/AU
L21         2387 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L17 OR L18 OR L19 OR L20)
L22           11 SEA FILE=CAPLUS ABB=ON  PLU=ON  L21 AND L10
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=> d .ca l14 1-14;d .ca l22 1-11

L14 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:547194 CAPLUS
DOCUMENT NUMBER: 145:55430
TITLE: Single-dose safety and pharmacokinetics of brecanavir, a novel human immunodeficiency virus protease inhibitor
AUTHOR(S): Ford, Susan L.; Reddy, Y. Sunila; Anderson, Maggie T.; Murray, Sharon C.; Fernandez, Pedro; Stein, Daniel S.; Johnson, Mark A.
CORPORATE SOURCE: GlaxoSmithKline, Research Triangle Park, NC, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2006), 50(6), 2201-2206
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 12 Jun 2006
AB Brecanavir (BCV, 640385) is a novel, potent protease inhibitor (PI) with low nanomolar 50% inhibitory concns. against PI-resistant human

immunodeficiency virus (HIV) in vitro. This phase I, double-blind, randomized, placebo-controlled, two-part single-dose study (first time with humans) was conducted to determine the safety, tolerability, and pharmacokinetics of BCV administered at 10 mg/mL in a tocopherol-polyethylene glycol succinate-polyethylene glycol 400-ethanol 50:40:10 solution In part 1 of the study, single oral doses of BCV ranged from 25 mg to 800 mg. In part 2, single oral doses of BCV ranged from 10 mg to 300 mg and were coadministered with 100-mg oral ritonavir (RTV) soft gel capsules. Single doses of BCV and BCV/RTV were generally well tolerated. There were no severe adverse events (SAEs), and no subject was withdrawn due to BCV. The most commonly reported drug-related AEs during both parts of the study combined were gastrointestinal disturbances (similar to placebo) and headache. BCV was readily absorbed following oral administration with mean times to maximum concentration from >1 h to 2.5 h in part 1
and from 1.5 h to 3 h in part 2. Administration of BCV without RTV resulted in BCV exposures predicted to be insufficient to inhibit PI-resistant virus based on in vitro data. Coadministration of 300 mg BCV with 100 mg RTV, however, significantly increased the plasma BCV area under the concentration-time curve and maximum concentration 26-fold and 11-fold, resp.,
achieving BCV concns. predicted to inhibit PI-resistant HIV.

CC 1-5 (Pharmacology)

IT Drug **resistance**
(antiviral; single-dose safety and pharmacokinetics of brecanavir, a novel human immunodeficiency virus protease inhibitor)

IT Antiviral agents
(**resistance** to; single-dose safety and pharmacokinetics of brecanavir, a novel human immunodeficiency virus protease inhibitor)

IT 155213-67-5, Ritonavir **313682-08-5**, Brecanavir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(single-dose safety and pharmacokinetics of brecanavir, a novel human immunodeficiency virus protease inhibitor)

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:270625 CAPLUS
DOCUMENT NUMBER: 144:266487
TITLE: Discovery of next generation inhibitors of HIV protease
AUTHOR(S): Spaltenstein, Andrew; Kazmierski, Wieslaw M.; Miller, John F.; Samano, Vicente
CORPORATE SOURCE: Division of Chemistry, MV CEDD, GlaxoSmithKline, Research Triangle Park, NC, 27709, USA
SOURCE: Current Topics in Medicinal Chemistry (Sharjah, United Arab Emirates) (2005), 5(16), 1589-1607
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

ED Entered STN: 23 Mar 2006

AB A review. Due to factors such as resistance and long-term side effects as well as dosing regimen-related adherence issues, HIV therapy is a constantly moving target. HIV-1 protease inhibitors had an immediate and dramatic impact on the outcome of HIV/AIDS when launched in late 1995, and the search for new and improved next generation mols. has been under way in many labs. At GlaxoSmithKline (GSK) and Vertex Pharmaceuticals, this effort focused on 2 key issues, patient compliance and viral resistance.

Using a water-solubilizing prodrug approach, the pill burden in delivering a protease inhibitor, Amprenavir, was dramatically decreased. By eliminating the large amts. of excipients necessary for the original soft-gel formulation, Fosamprenavir (Lexiva/Telzir) delivers the clin. efficacious dose of Amprenavir with 2 compact tablets per dose, compared to 8 gel capsules. The efforts to overcome viral resistance to 1st generation protease inhibitors by further elaborating the SAR of the Amprenavir and related scaffolds led to successive and dramatic improvements in wild-type antiviral potencies, and ultimately to the discovery of ultra-potent mols. with very favorable overall resistance profiles. The selection of GW640385 (Brecanavir - USAN approved only) as a clin. candidate and its progression into current phase 2 dose ranging studies represents the culmination of the effort toward the next generation protease inhibitors.

CC 1-0 (Pharmacology)
Section cross-reference(s): 14

IT AIDS (disease)
Drug discovery
Drug **resistance**
Human
(discovery of next generation inhibitors of HIV protease)

IT 161814-49-9, Amprenavir 226700-79-4, Fosamprenavir **313682-08-5**, Brecanavir
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(discovery of next generation inhibitors of HIV protease)

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:252581 CAPLUS
DOCUMENT NUMBER: 144:425067
TITLE: In vitro development of **resistance** to human immunodeficiency virus protease inhibitor GW640385
AUTHOR(S): Yates, P. J.; Hazen, R.; St. Clair, M.; Boone, L.; Tisdale, M.; Elston, R. C.
CORPORATE SOURCE: GlaxoSmithKline Inc., Stevenage, UK
SOURCE: Antimicrobial Agents and Chemotherapy (2006), 50(3), 1092-1095
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 20 Mar 2006

AB Development of in vitro resistance to GW640385, a new human immunodeficiency virus type 1 protease inhibitor, was studied. Variants characterized included one with <4-fold resistance and amino acid substitutions Q58E/A71V (protease) and P452K (Gag) and one with >50-fold resistance and amino acid substitutions L10F/G16E/E21K/A28S/M46I/F53L/A71V (protease) and L449F/P453T (Gag). The A28S substitution substantially reduced replication capacity.

CC 1-2 (Pharmacology)
Section cross-reference(s): 7

ST HIV1 virus GW64385 **resistance** protease gag mutation; sequence HIV1 virus protease gag GW64385 **resistance**

IT gag proteins
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(cleavage site; in vitro development of **resistance** to human immunodeficiency virus protease inhibitor GW640385)

IT Structure-activity relationship
(drug **resistance**; in vitro development of **resistance** to human immunodeficiency virus protease inhibitor GW640385)
IT Gene, microbial
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(gag; in vitro development of **resistance** to human immunodeficiency virus protease inhibitor GW640385)
IT Anti-AIDS agents
Drug **resistance**
Human immunodeficiency virus 1
Mutation
Protein sequences
(in vitro development of **resistance** to human immunodeficiency virus protease inhibitor GW640385)
IT Gene, microbial
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(pro; in vitro development of **resistance** to human immunodeficiency virus protease inhibitor GW640385)
IT 884544-94-9 884544-95-0 884544-96-1 884544-97-2 884544-98-3
884544-99-4 884545-00-0 884545-01-1 884545-02-2 884545-03-3
884545-04-4 884545-05-5 884545-06-6 884545-07-7 884545-08-8
884545-09-9 884545-10-2 884545-11-3 884545-12-4 884545-13-5
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884545-29-3 884545-30-6 884545-31-7 884545-32-8 884545-33-9
884545-34-0 884545-35-1 884545-36-2 884545-37-3 884545-38-4
884545-39-5 884545-40-8 884545-41-9 884545-42-0 884545-43-1
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884545-59-9 884545-60-2 884545-61-3 884545-62-4 884545-63-5
884545-64-6 884545-65-7 884545-66-8
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; in vitro development of **resistance** to human immunodeficiency virus protease inhibitor GW640385)
IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(in vitro development of **resistance** to human immunodeficiency virus protease inhibitor GW640385)
IT **313682-08-5**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro development of **resistance** to human immunodeficiency virus protease inhibitor GW640385)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:188865 CAPLUS
DOCUMENT NUMBER: 144:432712
TITLE: Ultra-potent P1 modified arylsulfonamide HIV protease inhibitors: The discovery of GW0385
AUTHOR(S): Miller, John F.; Andrews, C. Webster; Brieger, Michael; Furfine, Eric S.; Hale, Michael R.; Hanlon, Mary H.; Hazen, Richard J.; Kaldor, Istvan; McLean, Ed W.; Reynolds, David; Sammond, Douglas M.;

Spaltenstein, Andrew; Tung, Roger; Turner, Elizabeth M.; Xu, Robert X.; Sherrill, Ronald G.
CORPORATE SOURCE: GlaxoSmithKline, Research Triangle Park, NC, 27709, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(7), 1788-1794
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 02 Mar 2006
AB A novel series of P1 modified HIV protease inhibitors was synthesized and evaluated for in vitro antiviral activity against wild-type virus and protease inhibitor-resistant viruses. Optimization of the P1 moiety resulted in compds. with femtomolar enzyme activities and cellular antiviral activities in the low nanomolar range culminating in the identification of clin. candidate GW0385.
CC 28-5 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
IT Drug **resistance**
Pharmacokinetics
(preparation of the dioxabicyclooctyl thiazolylmethoxybenzyl-substituted (benzodioxolylsulfonylamino)propylcarbamate GW0385 as an anti-HIV agent and its pharmacokinetics and behavior in **resistant** HIV strains)
IT **313679-77-5P 313679-90-2P**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and pharmacokinetics of nonracemic dioxabicyclooctyl arylmethoxybenzyl-substituted (benzodioxolylsulfonylamino)propylcarbamates as potent HIV protease inhibitors and anti-HIV agents)
IT **313679-55-9P 884902-43-6P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of nonracemic dioxabicyclooctyl aryloxybenzyl- and arylmethoxybenzyl-substituted (benzodioxolylsulfonylamino)propylcarbamates as potent HIV protease inhibitors and anti-HIV agents)
IT **313679-83-3P 313679-89-9P 313682-06-3P**
313682-24-5P 884902-36-7P 884902-37-8P
884902-38-9P 884902-39-0P 884902-40-3P
884902-41-4P 884902-42-5P 884902-44-7P
884902-45-8P 884902-46-9P 884902-47-0P
884902-48-1P 884902-49-2P 884902-50-5P
884902-51-6P 884902-52-7P 884902-53-8P
884902-54-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of nonracemic dioxabicyclooctyl aryloxybenzyl- and arylmethoxybenzyl-substituted (benzodioxolylsulfonylamino)propylcarbamates as potent HIV protease inhibitors and anti-HIV agents)
IT **313679-57-1P** 313681-84-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of nonracemic dioxabicyclooctyl aryloxybenzyl- and arylmethoxybenzyl-substituted (benzodioxolylsulfonylamino)propylcarbamates as potent HIV protease inhibitors and anti-HIV agents)
IT **313682-08-5P**, GW0385
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

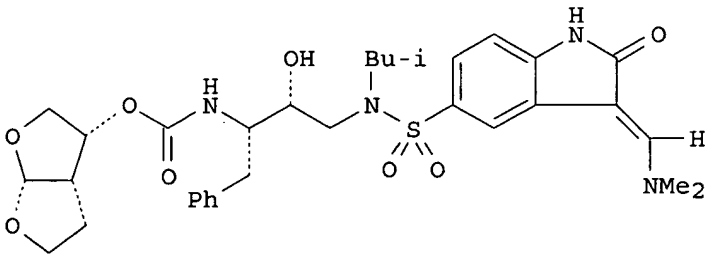
(preparation of the dioxabicyclooctyl thiazolylmethoxybenzyl-substituted (benzodioxolylsulfonylamino)propylcarbamate GW0385 as an anti-HIV agent and its pharmacokinetics and behavior in **resistant** HIV strains)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1021739 CAPLUS
DOCUMENT NUMBER: 143:326208
TITLE: Preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors
INVENTOR(S): Eissenstat, Michael; Guerassina, Tatiana
PATENT ASSIGNEE(S): Sequoia Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005087728	A1	20050922	WO 2005-US8381	20050311
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005209301	A1	20050922	US 2005-77135	20050311
PRIORITY APPLN. INFO.:			US 2004-552643P P	20040311

OTHER SOURCE(S): MARPAT 143:326208
ED Entered STN: 22 Sep 2005
GI



II

AB Title compds. X-A-B-A'-X' [X = 5-7 membered non-aromatic heterocycle; A = ZCZNH, ZCOCONH, ZSO2NH, etc.; Z = amino, O, S, etc.; B = syn-CH(D)CH(OH)CH2; D = alk(en/yn)yl; aryl, cycloalkyl, etc.; A' = ND'-E';

D' = alk(en/yn)yl, aryl, cycloalkyl, etc.; E' = CO, SO, SO2; X' = indolyl; I] are prepared For instance, II is prepared in several steps from 2-oxo-2,3-dihydro-1H-indol-5-sulfonyl chloride (preparation given), [1-benzyl-2-hydroxy-4-phenylbutyl]isobutylcarbamic acid benzyl ester, carbonic acid 2,5-dioxopyrrolidin-1-yl ester hexahydrofuro[2,3-b]furan-3-yl ester and DMF di-Me acetal. II has an IC50 = 93 nM for a recombinant wild type HIV protease. I are useful for treating HIV infections.

IC ICM C07D209-34

CC 27-11 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

ST **resistance** retroviral protease dipeptide isostere inhibitor prepn

IT Multidrug **resistance**
(HIV infection; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(aerosols, inhalants; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(buccal; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(injections, i.m.; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(injections, i.p.; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(injections, i.v.; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(injections, s.c.; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(intrathecal; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(liposomes; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(nasal; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(ophthalmic; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(oral; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(parenterals; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT AIDS (disease)
Anti-AIDS agents
Anti-infective agents
Human

Human immunodeficiency virus 1
Infection
(preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Amides, preparation
Esters, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prodrug; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(prodrugs; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(rectal; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(sublingual; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(transdermal; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT Drug delivery systems
(vaginal; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor, combination pharmaceutical; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT 9068-38-6, Reverse transcriptase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT **865104-28-5P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT **865104-29-6P 865104-30-9P 865104-31-0P**
865104-32-1P 865104-33-2P 865104-34-3P
865104-35-4P 865104-36-5P 865104-37-6P
865104-38-7P 865104-39-8P 865104-40-1P
865104-41-2P 865104-42-3P 865104-43-4P
865104-44-5P 865104-45-6P 865104-46-7P
865104-47-8P 865104-48-9P 865104-49-0P
865104-50-3P 865104-51-4P 865104-52-5P
865104-54-7P 865104-55-8P 865104-56-9P
865104-57-0P 865104-58-1P 865104-59-2P
865104-60-5P 865104-61-6P 865104-62-7P
865104-63-8P 865104-64-9P 865104-65-0P
865104-66-1P 865104-67-2P 865104-68-3P
865104-69-4P 865104-70-7P 865104-71-8P
865104-72-9P 865104-73-0P 865104-74-1P
865104-75-2P 865104-76-3P 865104-77-4P
865104-78-5P 865104-79-6P 865104-80-9P
865104-81-0P 865104-82-1P 865104-83-2P

865104-84-3P 865104-85-4P 865104-86-5P
865104-87-6P 865104-88-7P 865104-89-8P
865104-90-1P 865104-91-2P 865104-92-3P
865104-93-4P 865104-94-5P 865104-95-6P
865104-96-7P 865104-97-8P 865104-98-9P
865104-99-0P 865105-00-6P 865105-01-7P
865105-02-8P 865105-03-9P 865105-04-0P
865105-05-1P 865105-06-2P 865105-07-3P
865105-08-4P 865105-09-5P 865105-10-8P
865105-11-9P 865105-12-0P 865105-13-1P
865105-14-2P 865105-15-3P 865105-16-4P
865105-17-5P 865105-18-6P 865105-19-7P
865105-20-0P 865105-21-1P 865105-22-2P
865105-23-3P 865105-24-4P 865105-25-5P
865105-26-6P 865105-27-7P 865105-28-8P
865105-29-9P 865105-30-2P 865105-31-3P
865105-32-4P 865105-33-5P 865105-34-6P
865105-35-7P 865105-36-8P 865105-37-9P
865105-38-0P 865105-39-1P 865105-40-4P
865105-42-6P 865105-44-8P 865105-45-9P
865105-47-1P 865105-48-2P 865105-49-3P
865105-50-6P 865105-51-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT 59-48-3, 1,3-Dihydro-2-indolone 501-53-1, Benzyl chlorocarbonate 4637-24-5 5813-64-9, Neopentylamine 160232-08-6 253265-97-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

IT 160232-10-0P 199328-31-9P **664344-17-6P** 664344-42-7P 865105-52-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of diamino-mono-ol dipeptide isostere core based **resistance-repellent** retroviral protease inhibitors)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:589326 CAPLUS
DOCUMENT NUMBER: 143:267225
TITLE: Novel P1 chain-extended HIV protease inhibitors possessing potent anti-HIV activity and remarkable inverse antiviral **resistance** profiles
AUTHOR(S): Miller, John F.; Brieger, Michael; Furfine, Eric S.; Hazen, Richard J.; Kaldor, Istvan; Reynolds, David; Sherrill, Ronald G.; Spaltenstein, Andrew
CORPORATE SOURCE: GlaxoSmithKline, Research Triangle Park, NC, 27709, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2005), 15(15), 3496-3500
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 143:267225
ED Entered STN: 08 Jul 2005

AB A novel series of tyrosine-derived HIV protease inhibitors was synthesized and evaluated for in vitro antiviral activity against wild-type virus and two protease inhibitor-resistant viruses. All of the compds. had wild-type antiviral activities that were similar to or greater than several currently marketed HIV protease inhibitors. In addition, a number of compds. in this series were more potent against the drug-resistant mutant viruses than they were against wild-type virus.

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7

IT Anti-AIDS agents
Antiviral agents
Human
Human immunodeficiency virus
Peptidomimetics
(preparation of P1 chain-extended HIV protease inhibitors possessing potent anti-HIV activity and remarkable inverse antiviral **resistance** profiles)

IT 144114-21-6, Hiv protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of P1 chain-extended HIV protease inhibitors possessing potent anti-HIV activity and remarkable inverse antiviral **resistance** profiles)

IT **313680-07-8P 313680-24-9P**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of P1 chain-extended HIV protease inhibitors possessing potent anti-HIV activity and remarkable inverse antiviral **resistance** profiles)

IT **313680-01-2P 313680-03-4P 313680-05-6P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of P1 chain-extended HIV protease inhibitors possessing potent anti-HIV activity and remarkable inverse antiviral **resistance** profiles)

IT **313680-06-7P 313680-08-9P 313680-10-3P**
313680-11-4P 313680-25-0P 313680-32-9P
313680-33-0P 313680-34-1P 313680-35-2P
313680-36-3P 313680-38-5P 313680-40-9P
313681-90-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of P1 chain-extended HIV protease inhibitors possessing potent anti-HIV activity and remarkable inverse antiviral **resistance** profiles)

IT 78-81-9, Isobutylamine 79-22-1, Methyl chloroformate 79-44-7, Dimethylcarbamoyl chloride 593-71-5, Chloroiodomethane 624-83-9, Methyl isocyanate 7693-46-1, 4-Nitrophenyl chloroformate 26690-80-2 58885-58-8 75178-87-9 115010-10-1, 1,3-Benzodioxole-5-sulfonyl chloride 127132-32-5 156928-09-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of P1 chain-extended HIV protease inhibitors possessing potent anti-HIV activity and remarkable inverse antiviral **resistance** profiles)

IT 152438-62-5P 162536-84-7P 192725-55-6P 313679-53-7P
313679-55-9P 313679-57-1P 313680-00-1P
313680-02-3P 313680-04-5P 313681-20-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of P1 chain-extended HIV protease inhibitors possessing potent

anti-HIV activity and remarkable inverse antiviral **resistance** profiles)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:67041 CAPLUS
DOCUMENT NUMBER: 142:309248
TITLE: Design of HIV-1 Protease Inhibitors Active on Multidrug-**Resistant** Virus
AUTHOR(S): Surleraux, Dominique L. N. G.; De Kock, Herman A.; Verschueren, Wim G.; Pille, Geert M. E.; Maes, Louis J. R.; Peeters, Anik; Vendeville, Sandrine; De Meyer, Sandra; Azijn, Hilde; Pauwels, Rudi; De Bethune, Marie-Pierre; King, Nancy M.; Prabu-Jeyabalan, Moses; Schiffer, Celia A.; Wigerinck, Piet B. T. P.
CORPORATE SOURCE: Tibotec BVBA, Mechelen, B-2800, Belg.
SOURCE: Journal of Medicinal Chemistry (2005), 48(6), 1965-1973
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:309248
ED Entered STN: 26 Jan 2005
AB On the basis of structural data gathered during our ongoing HIV-1 protease inhibitors program, from which our clin. candidate TMC114 9 was selected, we have discovered new series of fused heteroarom. sulfonamides. The further extension into the P2' region was aimed at identifying new classes of compds. with an improved broad spectrum activity and acceptable pharmacokinetic properties. Several of these compds. display an exceptional broad spectrum activity against a panel of highly cross-resistant mutants. Certain members of these series exhibit favorable pharmacokinetic profiles in rat and dog. Crystal structures and mol. modeling were used to rationalize the broad spectrum profile resulting from the extension into the P2' pocket of the HIV-1 protease.
CC 1-5 (Pharmacology)
ST design HIV1 protease inhibitor multidrug **resistant** virus
IT Antiviral agents
Crystal structure
Human
Human immunodeficiency virus 1
(design of HIV-1 protease inhibitors active on multidrug-**resistant** virus)
IT **470704-42-8P 470704-47-3P 470704-54-2P**
470704-55-3P 473737-26-7P 473737-31-4P
473737-35-8P 473737-37-0P 473737-99-4P
473738-12-4P 473738-14-6P 475487-74-2P
475487-76-4P 660410-46-8P 848253-09-8P
848253-10-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(design of HIV-1 protease inhibitors active on multidrug-**resistant** virus)
IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir 161814-49-9, Amprenavir 174484-41-4, Tipranavir 192725-17-0, Lopinavir 198904-31-3, Atazanavir
473739-17-2 546085-67-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(design of HIV-1 protease inhibitors active on multidrug-**resistant** virus)

IT 74-89-5, Methanamine, reactions 108-00-9 109-55-7 109-81-9 124-40-3, reactions 615-22-5 4543-96-8 7154-73-6, 1-Pyrrolidineethanamine 32776-22-0 99114-68-8 160232-08-6 253265-97-3 470704-93-9 **848253-11-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(design of HIV-1 protease inhibitors active on multidrug-**resistant** virus)

IT 861213-55-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(design of HIV-1 protease inhibitors active on multidrug-**resistant** virus)

IT 7664-41-7, Ammonia, reactions 7719-09-7, Thionyl chloride 7790-94-5, Chlorosulfuric acid
RL: RGT (Reagent); RACT (Reactant or reagent)
(design of HIV-1 protease inhibitors active on multidrug-**resistant** virus)

IT 144114-21-6, HIV-1 protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; design of HIV-1 protease inhibitors active on multidrug-**resistant** virus)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:885959 CAPLUS
DOCUMENT NUMBER: 142:51214
TITLE: Inhibition of Wild-Type and Mutant Human Immunodeficiency Virus Type 1 Proteases by GW0385 and Other Arylsulfonamides
AUTHOR(S): Hanlon, Mary H.; Porter, David J. T.; Furfine, Eric S.; Spaltenstein, Andrew; Carter, H. Luke; Danger, Dana; Shu, Arthur Y. L.; Kaldor, Istvan W.; Miller, John F.; Samano, Vicente A.
CORPORATE SOURCE: GlaxoSmithKline, Research Triangle Park, PA, 19405, USA
SOURCE: Biochemistry (2004), 43(45), 14500-14507
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 26 Oct 2004
AB The arylsulfonamide derivs. described herein were such potent inhibitors of human immunodeficiency virus type 1 (HIV-1) protease (enzyme, E) that values for the inhibition consts. (Ki) could not be determined by conventional steady-state kinetic techniques (i.e., the minimal enzyme concentration usable for the activity assay was much greater than the value of the dissociation constant). Consequently, two alternative methods were developed for estimation of Ki values. The first method employed kinetic detns. of values for k1 and k-1, from which Ki was determined (k-1/k1). The second method was a competitive displacement assay used to determine binding affinities of other inhibitors relative to that of GW0385. In these assays, the inhibitor of unknown affinity was used to displace [3H]GW0385 from E·[3H]GW0385. From the concentration of E·[3H]GW0385 at equilibrium, the concns. of enzyme-bound and free inhibitors were calculated, and the ratio of the Ki value of the unknown to that of GW0385 was determined (Ki,unknown/Ki,GW0385). The values of k1 were calculated from data in which changes in the intrinsic

protein fluorescence of the enzyme associated with inhibitor binding were directly or indirectly monitored. In the case of saquinavir, the fluorescence changes associated with complex formation were large enough to monitor directly. The value of k1 for saquinavir was 62±2 μM-1 s-1. In the case of GW0385, the fluorescence changes associated with complex formation were too small to monitor directly. Consequently, the value of k1 was estimated from a competition experiment in which the effect of GW0385 on the binding of E to saquinavir was determined The value of k1 for GW0385 was estimated from these expts. to be 137±4 μM-1 s-1. Because E·[3H]GW0385 was stable in the standard buffer at room temperature for greater than 33 days, the value of the first-order rate constant for dissociation of E·[3H]GW0385 (k-1) could be estimated from the time-course for exchange of E·[3H]GW0385 with excess unlabeled GW0385. The value of k-1 calculated from these data was (2.1±0.1) + 10-6 s-1 (t1/2 = 91 h). The Ki value of wild-type HIV-1 protease for GW0385, calculated from these values for k1 and k-1, was 15±1 fM. Three multidrug resistant enzymes had Ki values for GW0385 that were less than 5 pM.

CC 7-3 (Enzymes)
Section cross-reference(s): 1

ST HIV1 protease inhibition GW0385 arylsulfonamide drug **resistance**

IT Drug **resistance**
(antiviral; inhibition of wild-type and drug-**resistant** mutant human immunodeficiency virus type 1 proteases by GW0385 and other arylsulfonamides monitored by fluorescence)

IT Anti-AIDS agents
Dissociation constant
Dissociation kinetics
Fluorescence
Hydrolysis
Structure-activity relationship
(inhibition of wild-type and drug-**resistant** mutant human immunodeficiency virus type 1 proteases by GW0385 and other arylsulfonamides monitored by fluorescence)

IT Enzyme kinetics
(of inhibition; inhibition of wild-type and drug-**resistant** mutant human immunodeficiency virus type 1 proteases by GW0385 and other arylsulfonamides monitored by fluorescence)

IT Antiviral agents
(**resistance** to; inhibition of wild-type and drug-**resistant** mutant human immunodeficiency virus type 1 proteases by GW0385 and other arylsulfonamides monitored by fluorescence)

IT **810687-58-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(as reactant in preparation of [3H]GW0385; inhibition of wild-type and drug-**resistant** mutant human immunodeficiency virus type 1 proteases by GW0385 and other arylsulfonamides monitored by fluorescence)

IT 9050-68-4, Sephadex G 10
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(behavior of HIV-1 proteases and [3H]GW0385 on G-10 resin; inhibition of wild-type and drug-**resistant** mutant human immunodeficiency virus type 1 proteases by GW0385 and other arylsulfonamides monitored by fluorescence)

IT 144114-21-6, HIV-1 protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of wild-type and drug-**resistant** mutant human immunodeficiency virus type 1 proteases by GW0385 and other arylsulfonamides monitored by fluorescence)

IT **810687-57-1P**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibition of wild-type and drug-**resistant** mutant human immunodeficiency virus type 1 proteases by GW0385 and other arylsulfonamides monitored by fluorescence)
IT 127779-20-8, Saquinavir 161814-49-9, Amprenavir **288292-27-3** **288292-51-3** **313679-77-5** **313679-90-2** **313682-08-5**, GW 0385
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(inhibition of wild-type and drug-**resistant** mutant human immunodeficiency virus type 1 proteases by GW0385 and other arylsulfonamides monitored by fluorescence)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:807698 CAPLUS
DOCUMENT NUMBER: 142:211389
TITLE: Discovery and Selection of TMC114, a Next Generation HIV-1 Protease Inhibitor
AUTHOR(S): Surleraux, Dominique L. N. G.; Tahri, Abdellah; Verschueren, Wim G.; Pille, Geert M. E.; de Kock, Herman A.; Jonckers, Tim H. M.; Peeters, Anik; De Meyer, Sandra; Azijn, Hilde; Pauwels, Rudi; de Bethune, Marie-Pierre; King, Nancy M.; Prabu-Jeyabalan, Moses; Schiffer, Celia A.; Wigerinck, Piet B. T. P.
CORPORATE SOURCE: Tibotec BVBA Generaal de Wittelaan L 11B 3, Mechelen, B-2800, Belg.
SOURCE: Journal of Medicinal Chemistry (2005), 48(6), 1813-1822
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:211389
ED Entered STN: 05 Oct 2004
AB The screening of known HIV-1 protease inhibitors against a panel of multidrug-resistant viruses revealed the potent activity of TMC126 on drug-resistant mutants. In comparison to amprenavir, the improved affinity of TMC126 is largely the result of one extra hydrogen bond to the backbone of the protein in the P2 pocket. Modification of the substitution pattern on the phenylsulfonamide P2' substituent of TMC126 created an interesting SAR, with the close analog TMC114 being found to have a similar antiviral activity against the mutant and the wild-type viruses. X-ray and thermodn. studies on both wild-type and mutant enzymes showed an extremely high enthalpy driven affinity of TMC114 for HIV-1 protease. In vitro selection of mutants resistant to TMC114 starting from wild-type virus proved to be extremely difficult; this was not the case for other close analogs. Therefore, the extra H-bond to the backbone in the P2 pocket cannot be the only explanation for the interesting antiviral profile of TMC114. Absorption studies in animals indicated that TMC114 has pharmacokinetic properties comparable to currently approved HIV-1 protease inhibitors.
CC 1-3 (Pharmacology)
IT Drug **resistance**
Structure-activity relationship

(antiviral; discovery and selection of TMC114, a next generation HIV-1 protease inhibitor)

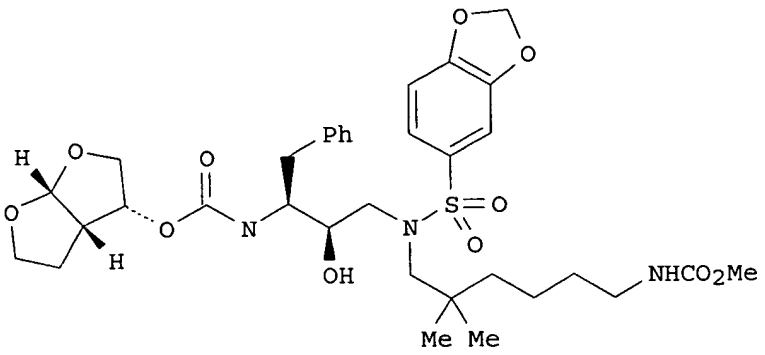
IT AIDS (disease)
Anti-AIDS agents
Drug design
Human
Molecular modeling
Multidrug **resistance**
(discovery and selection of TMC114, a next generation HIV-1 protease inhibitor)

IT Antiviral agents
(**resistance** to; discovery and selection of TMC114, a next generation HIV-1 protease inhibitor)

IT 206361-99-1DP, phosphate derivative 206361-99-1P, TMC114 206362-00-7P, TMC126 253266-00-1P **333798-27-9P** 546085-59-0P 546085-60-3P 553645-10-6P 799241-73-9P 799241-74-0P 799241-75-1P 799241-76-2P 799241-77-3P 799241-78-4P 799269-47-9P 799269-48-0P
RL: PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(discovery and selection of TMC114, a next generation HIV-1 protease inhibitor)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:99287 CAPLUS
DOCUMENT NUMBER: 140:339141
TITLE: Novel arylsulfonamides possessing sub-picomolar HIV protease activities and potent anti-HIV activity against wild-type and drug-**resistant** viral strains
AUTHOR(S): Miller, John F.; Furfine, Eric S.; Hanlon, Mary H.; Hazen, Richard J.; Ray, John A.; Robinson, Laurence; Samano, Vicente; Spaltenstein, Andrew
CORPORATE SOURCE: GlaxoSmithKline, Research Triangle Park, NC, 27709, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(4), 959-963
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:339141
ED Entered STN: 06 Feb 2004
GI



I

AB Furanofuryl analogs of the HIV protease inhibitor amprenavir such as I are prepared in which a terminally substituted n-alkyl group is appended to the N-iso-Bu group of amprenavir and in which the substituents on the N-arylsulfonyl moiety are varied. Some of the inhibitors such as I are found to have greatly enhanced inhibition of HIV protease; the amprenavir analogs also inhibit the growth of both wild-type and resistant strains of HIV and are more effective against the HIV strains than the currently marketed HIV protease inhibitors amprenavir, indinavir, and nelfinavir. E.g., I inhibits wild-type HIV protease with a Ki value of 0.014 pM, and inhibits wild-type and resistant strains of HIV with IC50 values of between 1.6 nM and 15 nM.

CC 27-7 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 10

ST furanofuryl analog amprenavir prepn HIV protease inhibitor; structure furanofuryl analog amprenavir HIV protease inhibition; HIV inhibitor analog amprenavir modified isobutyl arylsulfonyl group; activity amprenavir analog modified isobutyl arylsulfonyl group **resistant** HIV

IT Human
(preparation of furanofuryl amprenavir analogs with modifications at the N-arylsulfonyl and N-iso-Bu moieties which show improved HIV protease inhibition and inhibition of wild-type and **resistant** HIV strains)

IT Structure-activity relationship
(proteinase-inhibiting, HIV; preparation of furanofuryl amprenavir analogs with modifications at the N-arylsulfonyl and N-iso-Bu moieties which show improved HIV protease inhibition and inhibition of wild-type and **resistant** HIV strains)

IT 161814-49-9P, Amprenavir
RL: PNU (Preparation, unclassified); PREP (Preparation)
(furanofuryl analogs; preparation of furanofuryl amprenavir analogs with modifications at the N-arylsulfonyl and N-iso-Bu moieties which show improved HIV protease inhibition and inhibition of wild-type and **resistant** HIV strains)

IT 144114-21-6, HIV protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; preparation of furanofuryl amprenavir analogs with modifications at the N-arylsulfonyl and N-iso-Bu moieties which show improved HIV protease inhibition and inhibition of wild-type and **resistant** HIV strains)

IT **288292-03-5P 288292-18-2P 288292-24-0P**
288292-58-0P 288292-59-1P 288292-65-9P
288292-84-2P 288292-87-5P **288293-68-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL

(Biological study); PREP (Preparation)
(preparation of furanofuryl amprenavir analogs with modifications at the N-arylsulfonyl and N-iso-Bu moieties which show improved HIV protease inhibition and inhibition of wild-type and **resistant** HIV strains)

IT 51-50-3, N-(2-Chloroethyl)dibenzylamine 75-64-9, reactions 78-84-2, Isobutyraldehyde 109-70-6, 1-Bromo-3-chloropropane 4431-74-7, 3-Aminobenzenesulfonyl chloride 6140-61-0, 4-Cyano-2.2-dimethylbutanal 6940-78-9, 1-Bromo-4-chlorobutane 7693-46-1, 4-Nitrophenyl chloroformate 24939-24-0, p-Aminobenzenesulfonyl chloride 98737-29-2 115010-10-1, 1,3-Benzodioxole-5-sulfonyl chloride 156928-09-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of furanofuryl amprenavir analogs with modifications at the N-arylsulfonyl and N-iso-Bu moieties which show improved HIV protease inhibition and inhibition of wild-type and **resistant** HIV strains)

IT 52387-41-4P 87921-72-0P 147377-62-6P 162536-42-7P 162536-72-3P 165331-67-9P 192725-55-6P 288291-46-3P **288291-55-4P** **288291-99-6P** **288292-12-6P** **288292-37-5P** **288292-38-6P** 288292-42-2P 288292-43-3P 288295-80-7P 288296-23-1P 288296-24-2P 288296-32-2P **288296-33-3P** **288296-37-7P** 288296-72-0P **288296-75-3P** 288296-78-6P 681028-75-1P 681028-76-2P 681028-77-3P 681028-78-4P **681028-79-5P** 681028-80-8P 681028-81-9P 681028-82-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of furanofuryl amprenavir analogs with modifications at the N-arylsulfonyl and N-iso-Bu moieties which show improved HIV protease inhibition and inhibition of wild-type and **resistant** HIV strains)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:21007 CAPLUS
DOCUMENT NUMBER: 140:90648
TITLE: Mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**
INVENTOR(S): De Meyer, Sandra; Azijn, Hilde; De Bethune, Marie-pierre T. M. M. G.
PATENT ASSIGNEE(S): Tibotec Pharmaceuticals Ltd., Ire.
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004003817	A1	20040108	WO 2003-EP50277	20030630

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2490862	AA	20040108	CA 2003-2490862	20030630
AU 2003254500	A1	20040119	AU 2003-254500	20030630
EP 1520247	A1	20050406	EP 2003-761598	20030630
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005233312	A1	20051020	US 2004-519035	20041222
PRIORITY APPLN. INFO.:			US 2002-392753P	P 20020701
			WO 2003-EP50277	W 20030630

ED Entered STN: 11 Jan 2004

AB The present invention is directed to the field of nucleic acid diagnostics and the identification of base variation in target nucleic acid sequences. More particularly, the present invention relates to the use of such genotypic characterization of a target population of HIV and the subsequent association, i.e., correlation, of this information to phenotypic interpretation in order to correlate virus mutational profiles with drug resistance. The invention also relates to methods of utilizing the mutational profiles of the invention in drug development, i.e., drug discovery, drug design, drug modification, and therapy, treatment design, clin. management and diagnostic anal.

IC ICM G06F019-00
ICS C12Q001-70; C12N009-50

CC 10-5 (Microbial, Algal, and Fungal Biochemistry)
Section cross-reference(s): 1, 3, 7, 9

ST HIV1 protease mutation phenotype drug **resistance** diagnosis

IT Nucleic acids
RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(HIV-1 protease-encoding; mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT Drug **resistance**
(antiviral; mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT Computer application
Databases
(bioinformatic; mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT Diagnosis
(genetic, of viral drug **resistance**; mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT AIDS (disease)
Anti-AIDS agents
Bioinformatics
DNA shuffling
Drug discovery
Genotypes
Human
Human immunodeficiency virus
Human immunodeficiency virus 1
Mutation
Phenotypes
(mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT Probes (nucleic acid)
RL: ARG (Analytical reagent use); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT Antiviral agents

(**resistance** to; mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT Mutagenesis
(site-directed, deletion; mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT 56-40-6, Glycine, biological studies 56-45-1, L-Serine, biological studies 56-86-0, L-Glutamic acid, biological studies 56-87-1, L-Lysine, biological studies 72-19-5, L-Threonine, biological studies 73-32-5, L-Isoleucine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(-41, in mutant HIV-1 protease; mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT 144114-21-6, HIV-1 protease
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
(mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT 159989-64-7, Nelfinavir 206361-99-1 **473737-31-4**
RL: PAC (Pharmacological activity); BIOL (Biological study)
(mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

IT 193280-00-1
RL: PRP (Properties)
(unclaimed sequence; mutational profiles in HIV-1 protease correlated with phenotypic drug **resistance**)

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:931343 CAPLUS
DOCUMENT NUMBER: 140:704
TITLE: Broad-spectrum substituted benzisoxazole sulfonamide HIV protease inhibitors, preparation thereof, pharmaceutical compositions, diagnostic kits, and combinations with other antiretroviral agents
INVENTOR(S): Surleraux, Dominique Louis Nestor Ghislain; Vergouwen, Bernhard Joanna Bernard; De Kock, Herman Augustinus
PATENT ASSIGNEE(S): Tibotec Pharmaceuticals Ltd, Ire.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003097616	A1	20031127	WO 2003-EP50173	20030516
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2485903	AA	20031127	CA 2003-2485903	20030516
AU 2003238074	A1	20031202	AU 2003-238074	20030516

BR 2003010089	A	20050215	BR 2003-10089	20030516
EP 1517899	A1	20050330	EP 2003-735707	20030516
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005171173	A1	20050804	US 2003-514539	20030516
CN 1668605	A	20050914	CN 2003-816458	20030516
JP 2005527607	T2	20050915	JP 2004-505349	20030516
NZ 536496	A	20060630	NZ 2003-536496	20030516
NO 2004005444	A	20050216	NO 2004-5444	20041214
ZA 2004010156	A	20050905	ZA 2004-10156	20041215
PRIORITY APPLN. INFO.:			EP 2002-76957 A	20020517
			WO 2003-EP50173 W	20030516

OTHER SOURCE(S): MARPAT 140:704
ED Entered STN: 28 Nov 2003
AB The invention discloses benzisoxazole sulfonamide derivs. and the N-oxides, salts, stereoisomers, racemic mixts., prodrugs esters, and metabolites thereof. Also disclosed are their use as broad-spectrum HIV protease inhibitors, processes for their preparation, and pharmaceutical compns. and diagnostic kits comprising them. Further disclosed are combinations of the compds. of the invention with another antiretroviral agent, and their use in assays as reference compds. or as reagents.
IC ICM C07D261-20
ICS C07D493-04; C07D413-12; C07D417-12; A61K031-423; A61K031-427; A61P031-18; C07D307-00
CC 1-5 (Pharmacology)
Section cross-reference(s): 9, 28, 63
IT Drug **resistance**
(antiviral; benzisoxazole sulfonamide derivative HIV protease inhibitors, preparation, pharmaceutical compns., diagnostic kits, and combinations with other antiretroviral agents)
IT AIDS (disease)
Anti-AIDS agents
Antiviral agents
Drug bioavailability
Drug delivery systems
Human
Human immunodeficiency virus
Multidrug **resistance**
Retroviridae
(benzisoxazole sulfonamide derivative HIV protease inhibitors, preparation, pharmaceutical compns., diagnostic kits, and combinations with other antiretroviral agents)
IT Antiviral agents
(**resistance** to; benzisoxazole sulfonamide derivative HIV protease inhibitors, preparation, pharmaceutical compns., diagnostic kits, and combinations with other antiretroviral agents)
IT **627869-95-8P**
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(benzisoxazole sulfonamide derivative HIV protease inhibitors, preparation, pharmaceutical compns., diagnostic kits, and combinations with other antiretroviral agents)
IT 627869-96-9P 627869-98-1P 627869-99-2P **627870-00-2P**
627870-01-3P 627870-03-5P 627870-04-6P
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(benzisoxazole sulfonamide derivative HIV protease inhibitors, preparation, pharmaceutical compns., diagnostic kits, and combinations with other

antiretroviral agents)
IT **627869-81-2 627869-81-2D**, N-oxides and stereoisomers
627869-82-3 627869-82-3D, N-oxides and stereoisomers 627869-83-4
627869-83-4D, N-oxides and stereoisomers **627869-84-5**
627869-84-5D, N-oxides and stereoisomers 627869-85-6
627869-85-6D, N-oxides and stereoisomers 627869-86-7 627869-86-7D,
N-oxides and stereoisomers 627869-87-8 627869-87-8D, N-oxides and
stereoisomers **627869-88-9 627869-88-9D**, N-oxides and
stereoisomers **627869-89-0 627869-89-0D**, N-oxides and
stereoisomers **627869-90-3 627869-90-3D**, N-oxides and
stereoisomers **627869-91-4 627869-91-4D**, N-oxides and
stereoisomers
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity);
THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(benzisoxazole sulfonamide derivative HIV protease inhibitors, preparation,
pharmaceutical compns., diagnostic kits, and combinations with other
antiretroviral agents)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:472395 CAPLUS
DOCUMENT NUMBER: 139:47200
TITLE: Combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections
INVENTOR(S): Van Der Geest, Ronald; Stoffels, Paul; Groen, Cornelis; Jochmans, Dirk Edward Desire
PATENT ASSIGNEE(S): Tibotec Pharmaceuticals Ltd., Ire.
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003049746	A2	20030619	WO 2002-EP14277	20021212
WO 2003049746	A3	20031231		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2469343	AA	20030619	CA 2002-2469343	20021212
AU 2002358713	A1	20030623	AU 2002-358713	20021212
EP 1458447	A2	20040922	EP 2002-793018	20021212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002015043	A	20041103	BR 2002-15043	20021212
CN 1604803	A	20050406	CN 2002-824911	20021212
JP 2005511723	T2	20050428	JP 2003-550795	20021212
US 2005119338	A1	20050602	US 2003-498024	20021212
ZA 2004004633	A	20050901	ZA 2004-4633	20040610
NO 2004002666	A	20040909	NO 2004-2666	20040624

PRIORITY APPLN. INFO.: EP 2001-204841 A 20011212
WO 2002-EP14277 W 20021212

OTHER SOURCE(S): MARPAT 139:47200

ED Entered STN: 20 Jun 2003

AB The present invention relates to a method for improving the pharmacokinetics of hexahydrofuro[2,3-b]furanyl containing HIV protease inhibitors comprising administering to a human in need thereof a combination of a therapeutically effective amount of a hexahydrofuro[2,3-b]furanyl containing HIV protease inhibitor, and a therapeutically effective amount of a cytochrome P450 inhibitor.

IC ICM A61K031-635

CC 1-12 (Pharmacology)

IT Drug **resistance**
(antiviral; combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

IT AIDS (disease)
Anti-AIDS agents
Antiviral agents
Drug interactions
Human
Human immunodeficiency virus
Multidrug **resistance**
Retroviridae
(combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

IT Drug delivery systems
(excipients; combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

IT Drug interactions
(pharmacokinetic; combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

IT Antiviral agents
(**resistance** to; combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

IT Infection
(viral, retrovirus; combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

IT 206361-99-1 206361-99-1D, esters 206362-00-7 206362-00-7D, esters
253266-01-2 253266-01-2D, esters **333798-27-9**
333798-27-9D, esters **470704-39-3** **470704-39-3D**,
esters **470704-42-8** **470704-42-8D**, esters
470704-44-0 **470704-44-0D**, esters **470704-47-3**
470704-47-3D, esters **470704-54-2** **470704-54-2D**,
esters **470704-55-3** **470704-55-3D**, esters
473737-29-0 **473737-29-0D**, esters **473737-30-3**
473737-30-3D, esters **473737-31-4** **473737-31-4D**,
esters **473737-33-6** **473737-33-6D**, esters
473737-35-8 **473737-35-8D**, esters **473737-37-0**
473737-37-0D, esters **473737-39-2** **473737-39-2D**,
esters **473737-41-6** **473737-41-6D**, esters

473737-42-7 473737-42-7D, esters 473737-43-8
473737-43-8D, esters 473737-44-9 473737-44-9D,
esters 473774-92-4 473774-92-4D, esters
473774-93-5 473774-93-5D, esters 473774-94-6
473774-94-6D, esters 473774-95-7 473774-95-7D,
esters 473774-96-8 473774-96-8D, esters
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RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of cytochrome P 450 inhibitors and HIV protease inhibitors
to treat retrovirus infections and increase pharmacokinetics of HIV
protease inhibitors in relation to **resistance**)

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546087-06-3D, esters 546087-07-4 546087-07-4D,
esters 546087-08-5 546087-08-5D, esters
546087-09-6 546087-09-6D, esters 546087-10-9
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esters 546087-12-1 546087-12-1D, esters
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of cytochrome P 450 inhibitors and HIV protease inhibitors
to treat retrovirus infections and increase pharmacokinetics of HIV
protease inhibitors in relation to **resistance**)

IT 7380-40-7, Bergamottin 51481-61-9, Cimetidine 65277-42-1, Ketoconazole

127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir
159989-64-7, Nelfinavir 161814-49-9, Amprenavir 192725-17-0, Lopinavir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

IT 9035-51-2, Cytochrome P 450, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cytochrome P 450, inhibitors; combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

IT 144114-21-6, Retropepsin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combination of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

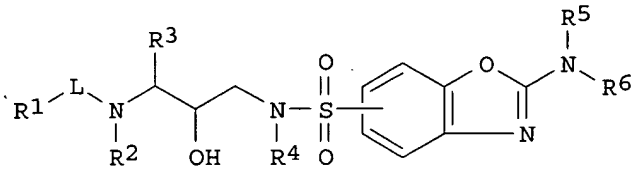
IT 546085-99-8
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nation of cytochrome P 450 inhibitors and HIV protease inhibitors to treat retrovirus infections and increase pharmacokinetics of HIV protease inhibitors in relation to **resistance**)

L14 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:888736 CAPLUS
DOCUMENT NUMBER: 137:384835
TITLE: Preparation of 2-amino-benzoxazole sulfonamide as broad-spectrum HIV protease inhibitors
INVENTOR(S): Surleraux, Dominique Louis Nestor Ghislain; Vendeville, Sandrine Marie Helene; Verschueren, Wim Gaston; De Bethune, Marie-Pierre T. M. M. G.; De Kock, Herman Augustinus; Tahri, Abdellah
PATENT ASSIGNEE(S): Tibotec Pharmaceuticals Ltd., Ire.
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092595	A1	20021121	WO 2002-EP5212	20020510
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2444895	AA	20021121	CA 2002-2444895	20020510
EP 1387842	A1	20040211	EP 2002-735354	20020510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
EE 200300547	A	20040216	EE 2003-547	20020510

BR 2002009594	A	20040330	BR 2002-9594		20020510
CN 1507446	A	20040623	CN 2002-809741		20020510
JP 2004534757	T2	20041118	JP 2002-589479		20020510
NZ 529250	A	20050527	NZ 2002-529250		20020510
ZA 2003007799	A	20050106	ZA 2003-7799		20031006
US 2004106661	A1	20040603	US 2003-474485		20031009
BG 108309	A	20041230	BG 2003-108309		20031103
PRIORITY APPLN. INFO.:			EP 2001-201732	A	20010511
			WO 2002-EP5212	W	20020510

OTHER SOURCE(S): MARPAT 137:384835
ED Entered STN: 22 Nov 2002
GI



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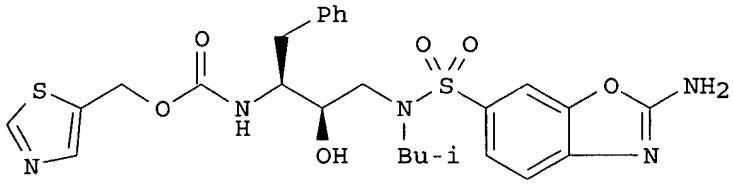

II

AB Title compds. I [R1, R8 = H, alkyl, alkenyl, arylalkyl, cycloalkyl, aryl, heterocyclyl, etc.; R2 = H, alkyl; L = CO, OCO, NR8CO, etc.; R3 = alkyl, cycloalkyl, aryl, etc.; R4 = H, alkoxycarbonyl, carboxy, aminocarbonyl, cycloalkyl, etc.; R5-6 = H, alkyl], N-oxides, stereoisomers, metabolites and prodrugs thereof were prepared For instance, II was prepared from the corresponding diamine (preparation described), N,N'-disuccinimidylcarbonate and 5-hydroxymethylthiazole (CH2Cl2, 6 h). Compds. of the invention are effective in inhibiting a broad range of mutant HIV strains; II had pEC50 = 8.18 against HIV-1 (Lai strain).

IC ICM C07D413-12
ICS C07D493-04; C07D417-12; C07D263-58; C07D498-04; C07D513-04; C07D413-14; C07D417-14; A61K031-423; C07D491-04

CC 28-6 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

IT AIDS (disease)
Anti-AIDS agents
Human
Human immunodeficiency virus
Multidrug **resistance**
(2-amino-benzoxazole sulfonamide as broad-spectrum HIV protease inhibitors)

IT 470704-98-4P **475487-53-7P** 475487-58-2P 475487-60-6P
475487-63-9P 475487-65-1P 475487-67-3P 475487-69-5P 475487-72-0P

475487-74-2P 475487-76-4P 475487-79-7P
475487-82-2P 475487-85-5P 475487-88-8P 475487-91-3P 475487-94-6P
475487-96-8P 475487-98-0P 475488-00-7P 475488-02-9P 475488-04-1P
475488-06-3P **475488-08-5P 475488-10-9P** 475488-14-3P
475488-17-6P 475488-19-8P 475488-21-2P 475488-25-6P 475488-27-8P
475488-29-0P 475488-31-4P **475488-33-6P 475488-36-9P**
475488-38-1P 475488-41-6P 475488-43-8P 475488-46-1P
475488-49-4P 475488-51-8P 475488-53-0P 475488-56-3P 475488-59-6P
475488-62-1P 475488-65-4P 475488-68-7P 475488-72-3P 475488-75-6P
475488-79-0P 475488-84-7P 475488-88-1P 475488-92-7P
475488-96-1P **475976-40-0P 475976-41-1P**
475976-42-2P 475976-43-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 2-amino-benzoxazole sulfonamide as broad-spectrum HIV protease inhibitors)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1240823 CAPLUS
DOCUMENT NUMBER: 144:6777
TITLE: Preparation of heterocyclyl sulfonylaminobenzylhydroxypropylcarbamates as HIV protease inhibitors
INVENTOR(S): **Eissenstat, Michael**; Delahanty, Greg; Topin, Andrey; Rajendran, Gnana Ravi
PATENT ASSIGNEE(S): Sequoia Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005110428	A2	20051124	WO 2005-US16056	20050509
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005267074	A1	20051201	US 2005-124056	20050509
PRIORITY APPLN. INFO.:			US 2004-568935P P	20040507

OTHER SOURCE(S): MARPAT 144:6777
ED Entered STN: 24 Nov 2005
GI

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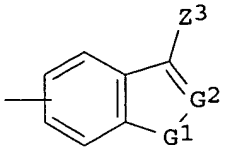
Q^2 = 

AB XABA1X1 [X = (substituted) (fused) (bridged) 5-7 membered heterocyclyl containing ≥1 O, N, S, P; A = CONH, COCONH, SO2NH, etc.; B = Q1; D = (substituted) alkyl, alkenyl, alkynyl, aryl, cycloalkyl, aralkyl; A1 = ND1E1; D1 = (substituted) alkyl, alkenyl, alkynyl, aryl, cycloalkyl, aralkyl; E1 = CO, SO2; X1 = (substituted) Q2; G1 = NH, O; G2 = CZ2, N; Z2 = H, halo, (substituted) alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, etc.; Z3 = Z2, haloalkyl, etc.], were prepared Thus, (1-benzyl-2-hydroxy-3-isobutylaminopropyl)carbamic acid hexahydrofuro[2,3-b]furan-3-yl ester, benzofuran-5-sulfonyl chloride, and aqueous NaHCO3 were stirred together for 16 h in CH2Cl2 to give 98.5% [3-[(benzofuran-5-sulfonyl)isobutylamino]-1-benzyl-2-hydroxypropyl]carbamic acid hexahydrofuro[2,3-b]furan-3-yl ester. The latter showed a Ki = <0.10 nM.

IC ICM A61K031-665
ICS A61K031-353; A61K031-343; C07D493-02

CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27, 63

IT **546085-74-9P 869885-44-9P 869885-45-0P**
869885-46-1P 869885-47-2P 869885-48-3P
869885-49-4P 869885-50-7P 869885-51-8P
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869989-09-3P 869989-10-6P 869989-11-7P
869989-12-8P 869989-13-9P 869989-14-0P
869989-15-1P 869989-16-2P 869989-17-3P
869989-19-5P 869989-20-8P 869989-21-9P
869989-23-1P 869989-25-3P 869989-27-5P
869989-28-6P 869989-29-7P 869989-30-0P
869989-31-1P 869989-32-2P 869989-33-3P
869989-34-4P 869989-35-5P 869989-36-6P
869989-37-7P 869989-38-8P 869989-39-9P
869989-40-2P 869989-59-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclyl sulfonylaminobenzylhydroxypropylcarbamates as HIV protease inhibitors)

IT 62-53-3, Aniline, reactions 62-56-6, Thiourea, reactions 66-25-1, Hexanal 74-89-5, Methylamine, reactions 75-04-7, Ethylamine, reactions 75-31-0, Isopropylamine, reactions 75-33-2, 2-Propanethiol 75-36-5, Acetyl chloride 75-89-8 75-98-9, Trimethylacetic acid 78-93-3, 2-Butanone, reactions 79-09-4, Propionic acid, reactions 79-31-2, Isobutyric acid 88-14-2, 2-Furoic acid 96-22-0, 3-Pentanone 98-59-9, p-Toluenesulfonyl chloride 98-88-4, Benzoyl chloride 100-46-9, Benzylamine, reactions 100-52-7, Benzaldehyde, reactions 100-53-8, Benzyl mercaptan 103-46-8 105-36-2, Ethyl bromoacetate 107-87-9, 2-Pentanone 108-24-7, Acetic anhydride 108-94-1, Cyclohexanone, reactions 108-98-5, Benzenethiol, reactions 109-61-5, Propyl chloroformate 109-73-9, n-Butylamine, reactions 109-79-5, 1-Butanethiol 109-85-3, 2-Methoxyethylamine 109-89-7, Diethylamine, reactions 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 123-38-6, Propionaldehyde, reactions 123-56-8, Succinimide 123-72-8, Butyraldehyde 123-75-1, Pyrrolidine, reactions 124-63-0, Methanesulfonyl chloride 288-32-4, Imidazole, reactions 407-25-0, Trifluoroacetic anhydride 422-03-7, 2,2,3,3,3-Pentafluoropropylamine 422-64-0 496-16-2, 2,3-Dihydrobenzofuran 501-81-5, 3-Pyridylacetic acid 506-59-2, Dimethylamine hydrochloride 527-69-5, 2-Furoyl chloride 541-41-3, Ethyl chloroformate 594-44-5, Ethanesulfonyl chloride 617-35-6, Ethyl pyruvate 624-78-2, N-Methylethylamine 630-19-3, Trimethylacetaldehyde 753-90-2, 2,2,2-Trifluoroethylamine 824-79-3, p-Toluenesulfinic acid sodium salt 924-44-7, Ethyl glyoxylate 1003-03-8, Cyclopentylamine 1069-72-3, 2-Bromo-N,N-diethylethylamine hydrobromide 1138-80-3 1544-53-2, 2,2,2-Trifluoroethanethiol 1758-46-9, 2-Phenoxyethylamine 2528-61-2, Heptanoyl chloride 2706-56-1, 2-(2-Aminoethyl)pyridine 3176-62-3, 3-Methylindazole 3218-02-8, Cyclohexanemethanamine 3731-51-9, 2-(Aminomethyl)pyridine 6456-74-2 7663-77-6, 1-(3-Aminopropyl)-2-pyrrolidinone 10147-37-2, Isopropylsulfonyl chloride 10400-19-8, Nicotinoyl chloride 13524-73-7, 3-Methyl-2,3-dihydro-benzofuran 15159-40-7, 4-Morpholinecarbonyl chloride 20277-69-4, Sodium methanesulfinate 21539-47-9,

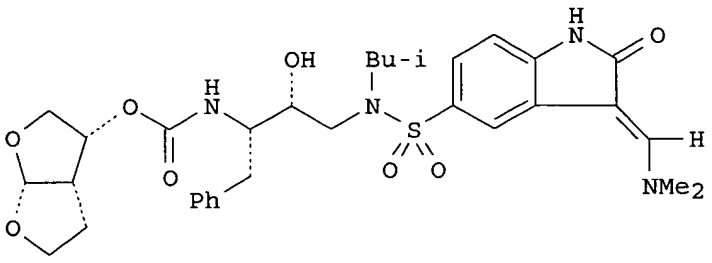
3-(Ethylamino)propionitrile 24424-99-5, Di-tert-butyl dicarbonate 29921-57-1, Isopropyl bromoacetate 36489-03-9, 2-(Ethylthio)ethylamine 37798-08-6, (Benzofuran-5-ylmethyl)amine 37912-62-2, Succinimide sodium salt 37924-67-7 57260-73-8 103694-26-4, 4-Aminomethyl-2-methylthiazole 152685-13-7 160232-08-6 253265-97-3 351003-23-1, 4-Fluoro-3-cyanobenzenesulfonyl chloride **869885-67-6** 869885-68-7, 2-Methyl-benzofuran-5-sulfonyl chloride 869885-69-8, 3-Methyl-benzofuran-5-sulfonyl chloride 869885-70-1, 2-Bromomethyl-benzofuran-5-sulfonyl chloride 869885-71-2, 3-Methylbenzisoxazole-5-sulfonyl chloride 869885-72-3 869885-73-4 869885-74-5, 3-Chloroindazole-5-sulfonyl chloride 869885-75-6, 3-(Bromomethyl)indazole-5-sulfonyl chloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of heterocyclyl sulfonylaminobenzylhydroxypropylcarbamates as HIV protease inhibitors)

IT 37924-85-9P 115010-11-2P 159305-11-0P 160232-10-0P 664344-42-7P 865105-52-8P 869885-60-9P, 5-Benzofuransulfonyl chloride 869885-61-0P 869885-62-1P 869885-63-2P 869885-64-3P **869885-65-4P** 869885-66-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of heterocyclyl sulfonylaminobenzylhydroxypropylcarbamates as HIV protease inhibitors)

L22 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1021739 CAPLUS
DOCUMENT NUMBER: 143:326208
TITLE: Preparation of diamino-mono-ol dipeptide isostere core based resistance-repellent retroviral protease inhibitors
INVENTOR(S): **Eissenstat, Michael**; Guerassina, Tatiana
PATENT ASSIGNEE(S): Sequoia Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005087728	A1	20050922	WO 2005-US8381		20050311
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2005209301	A1	20050922	US 2005-77135		20050311
PRIORITY APPLN. INFO.:			US 2004-552643P	P	20040311

OTHER SOURCE(S): MARPAT 143:326208
ED Entered STN: 22 Sep 2005
GI



II

AB Title compds. X-A-B-A'-X' [X = 5-7 membered non-aromatic heterocycle; A = ZCZNH, ZCOCONH, ZSO2NH, etc.; Z = amino, O, S, etc.; B = syn-CH(D)CH(OH)CH2; D = alk(en/yn)yl; aryl, cycloalkyl, etc.; A' = ND'-E'; D' = alk(en/yn)yl, aryl, cycloalkyl, etc.; E' = CO, SO, SO2; X' = indolyl; I] are prepared For instance, II is prepared in several steps from 2-oxo-2,3-dihydro-1H-indol-5-sulfonyl chloride (preparation given), [1-benzyl-2-hydroxy-4-phenylbutyl]isobutylcarbamic acid benzyl ester, carbonic acid 2,5-dioxopyrrolidin-1-yl ester hexahydrofuro[2,3-b]furan-3-yl ester and DMF di-Me acetal. II has an IC50 = 93 nM for a recombinant wild type HIV protease. I are useful for treating HIV infections.

IC ICM C07D209-34

CC 27-11 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

IT **865104-28-5P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of diamino-mono-ol dipeptide isostere core based resistance-repellent retroviral protease inhibitors)

IT **865104-29-6P 865104-30-9P 865104-31-0P**
865104-32-1P 865104-33-2P 865104-34-3P
865104-35-4P 865104-36-5P 865104-37-6P
865104-38-7P 865104-39-8P 865104-40-1P
865104-41-2P 865104-42-3P 865104-43-4P
865104-44-5P 865104-45-6P 865104-46-7P
865104-47-8P 865104-48-9P 865104-49-0P
865104-50-3P 865104-51-4P 865104-52-5P
865104-54-7P 865104-55-8P 865104-56-9P
865104-57-0P 865104-58-1P 865104-59-2P
865104-60-5P 865104-61-6P 865104-62-7P
865104-63-8P 865104-64-9P 865104-65-0P
865104-66-1P 865104-67-2P 865104-68-3P
865104-69-4P 865104-70-7P 865104-71-8P
865104-72-9P 865104-73-0P 865104-74-1P
865104-75-2P 865104-76-3P 865104-77-4P
865104-78-5P 865104-79-6P 865104-80-9P
865104-81-0P 865104-82-1P 865104-83-2P
865104-84-3P 865104-85-4P 865104-86-5P
865104-87-6P 865104-88-7P 865104-89-8P
865104-90-1P 865104-91-2P 865104-92-3P
865104-93-4P 865104-94-5P 865104-95-6P
865104-96-7P 865104-97-8P 865104-98-9P
865104-99-0P 865105-00-6P 865105-01-7P
865105-02-8P 865105-03-9P 865105-04-0P
865105-05-1P 865105-06-2P 865105-07-3P
865105-08-4P 865105-09-5P 865105-10-8P
865105-11-9P 865105-12-0P 865105-13-1P
865105-14-2P 865105-15-3P 865105-16-4P

865105-17-5P 865105-18-6P 865105-19-7P
865105-20-0P 865105-21-1P 865105-22-2P
865105-23-3P 865105-24-4P 865105-25-5P
865105-26-6P 865105-27-7P 865105-28-8P
865105-29-9P 865105-30-2P 865105-31-3P
865105-32-4P 865105-33-5P 865105-34-6P
865105-35-7P 865105-36-8P 865105-37-9P
865105-38-0P 865105-39-1P 865105-40-4P
865105-42-6P 865105-44-8P 865105-45-9P
865105-47-1P 865105-48-2P 865105-49-3P
865105-50-6P 865105-51-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diamino-mono-ol dipeptide isostere core based resistance-repellent retroviral protease inhibitors)

IT 160232-10-0P 199328-31-9P **664344-17-6P** 664344-42-7P
865105-52-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of diamino-mono-ol dipeptide isostere core based resistance-repellent retroviral protease inhibitors)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:960458 CAPLUS
DOCUMENT NUMBER: 140:138738
TITLE: Lessons in Molecular Recognition: The Effects of Ligand and Protein Flexibility on Molecular Docking Accuracy
AUTHOR(S): **Erickson, Jon A.**; Jalaie, Mehran; Robertson, Daniel H.; Lewis, Richard A.; Vieth, Michal
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Journal of Medicinal Chemistry (2004), 47(1), 45-55
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 10 Dec 2003
AB The key to success for computational tools used in structure-based drug design is the ability to accurately place or "dock" a ligand in the binding pocket of the target of interest. In this report we examine the effect of several factors on docking accuracy, including ligand and protein flexibility. To examine ligand flexibility in an unbiased fashion, a test set of 41 ligand-protein co-complex x-ray structures were assembled that represent a diversity of size, flexibility, and polarity with respect to the ligands. Four docking algorithms, DOCK, FlexX, GOLD, and CDOCKER, were applied to the test set, and the results were examined in terms of the ability to reproduce x-ray ligand positions within 2.0Å heavy atom root-mean-square deviation. Overall, each method performed well (>50% accuracy) but for all methods it was found that docking accuracy decreased substantially for ligands with eight or more rotatable bonds. Only CDOCKER was able to accurately dock most of those ligands with eight or more rotatable bonds (71% accuracy rate). A second test set of structures was gathered to examine how protein flexibility influences docking accuracy. CDOCKER was applied to x-ray structures of trypsin, thrombin, and HIV-1-protease, using protein structures bound to several ligands and also the unbound (apo) form. Docking expts. of each ligand to

one "average" structure and to the apo form were carried out, and the results were compared to docking each ligand back to its originating structure. The results show that docking accuracy falls off dramatically if one uses an average or apo structure. In fact, it is shown that the drop in docking accuracy mirrors the degree to which the protein moves upon ligand binding.

CC 1-3 (Pharmacology)

IT 57-10-3, Hexadecanoic acid, biological studies 57-83-0, Pregn-4-ene-3,20-dione, biological studies 58-85-5 59-05-2 71-00-1, L-Histidine, biological studies 73-40-5 92-62-6, 3,6-Acridinediamine 140-75-0 155-09-9 571-31-3 618-39-3, Benzenecarboximidamide 921-62-0 3218-02-8, Cyclohexanemethanamine 3646-73-9, α-D-Galactopyranose 3918-94-3 7296-55-1, α-L-Arabinopyranose 13147-57-4 13214-66-9, Benzenebutanamine 20762-30-5 37553-80-3 39281-68-0, α-L-Idopyranose 41017-96-3 55381-72-1 74863-84-6 86845-59-2 87495-31-6 117091-16-4 126333-28-6 134807-58-2 134878-17-4 138460-25-0 141396-10-3 144141-70-8 147318-81-8 147666-22-6 148982-38-1 148993-96-8 149379-09-9 150057-48-0 150348-92-8 150378-17-9 150612-55-8 150612-57-0 150654-53-8 151337-79-0 158341-94-7 **161814-49-9** 161897-65-0 162021-00-3 162021-02-5 162168-92-5 162427-45-4 168049-23-8 168112-62-7 171858-52-9 174960-52-2 175417-73-9 179745-65-4 180187-97-7 181367-23-7 184955-11-1 193958-35-9 194292-88-1 195715-81-2 214151-47-0 218304-65-5 218304-68-8 226892-37-1 227081-69-8 602284-37-7 637768-08-2 651355-59-8 651355-60-1 651355-64-5 651355-66-7 651355-68-9 651355-75-8 651355-77-0 651356-01-3 651356-07-9 651356-10-4 651356-13-7 651356-15-9 651356-17-1 651356-19-3 651356-21-7 651356-24-0 651356-27-3 651736-67-3

RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(mol. recognition, structure-property relationship, ligand binding and protein flexibility on mol. docking accuracy)

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:610435 CAPLUS

DOCUMENT NUMBER: 139:159902

TITLE: Resistance-repellent retroviral protease inhibitors

INVENTOR(S): **Erickson, John W.; Eissenstat, Michael; Silva, Abelardo; Gulnik, Sergei**

PATENT ASSIGNEE(S): Sequoia Pharmaceuticals, USA

SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003064406	A1	20030807	WO 2003-US254	20030107

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2473231	AA	20030807	CA 2003-2473231		20030107
US 2003171423	A1	20030911	US 2003-337349		20030107
US 2004009890	A1	20040115	US 2003-337699		20030107
EP 1483254	A1	20041208	EP 2003-723624		20030107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
US 2005107342	A1	20050519	US 2003-500888		20030107
ZA 2004005528	A	20050712	ZA 2004-5528		20040713
PRIORITY APPLN. INFO.:			US 2002-344788P	P	20020107
			US 2002-383575P	P	20020529
			WO 2003-US254	W	20030107

OTHER SOURCE(S): MARPAT 139:159902

ED Entered STN: 08 Aug 2003

AB Resistance-repellent and multidrug resistant retroviral protease inhibitors are provided. Pharmaceutical composition comprising such compds., and methods of using such compds. to treat HIV infections in mammals, are also provided. More particularly, the invention provides HIV protease inhibitors represented by the formula I: X-A-B-A'-X' where X is a moiety that contains ≥2 H bond acceptors capable of interacting with the backbone NH atoms of Asp29 and Asp30 of an HIV protease; A is a 2-6 atom linker that contains ≥ 1 H bond acceptor that interacts with the flap water, and 1 H bond donor that interacts with the backbone CO atom of residue 27; B contains 1-3 atoms that can form H bonds with either or both carboxylate side chain O of Asp25 and Asp 125 of said protease; A' is a 2-6 atom linker that contains ≤ 1 H bond acceptor that interacts with the flap water; and X' is a moiety that can form ≥ 1 H bonds with the backbone NH atoms of residues 129 and/or 130. The invention also provides a compound as described above, bound in a complex with wild type or drug resistant mutant forms of HIV-1 protease. The composition may further comprise an addnl. HIV protease inhibitor and/or an HIV reverse transcriptase inhibitor.

IC ICM C07D307-93
ICS A61K031-34

CC 1-5 (Pharmacology)

IT **206362-00-7**, UIC-94003
RL: CPS (Chemical process); DMA (Drug mechanism of action); PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(resistance-repellent retroviral protease inhibitors)

IT 144114-21-6D, HIV-1 protease, complexed with resistance-repellent inhibitor UIC-94003 **206362-00-7D**, UIC-94003, complexed with HIV-1 protease
RL: PRP (Properties)
(resistance-repellent retroviral protease inhibitors)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:551345 CAPLUS

DOCUMENT NUMBER: 139:95438

TITLE: Broad spectrum microbial and neoplasmic protein inhibitors

INVENTOR(S): **Erickson, John W.; Eissenstat, Michael; Silva, Abelardo; Gulnik, Sergei**

PATENT ASSIGNEE(S): Sequoia Pharmaceuticals, USA
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057173	A2	20030717	WO 2003-US415	20030107
WO 2003057173	A3	20031120		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2472580	AA	20030717	CA 2003-2472580	20030107
AU 2003202914	A1	20030724	AU 2003-202914	20030107
US 2003171423	A1	20030911	US 2003-337349	20030107
US 2004009890	A1	20040115	US 2003-337699	20030107
EP 1472536	A2	20041103	EP 2003-702026	20030107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
ZA 2004005528	A	20050712	ZA 2004-5528	20040713
PRIORITY APPLN. INFO.:			US 2002-344788P P	20020107
			US 2002-383575P P	20020529
			WO 2003-US415 W	20030107

ED Entered STN: 18 Jul 2003
AB The invention features a method of designing broad spectrum inhibitors (e.g., of HIV-1 protease) using structural data, compns. having broad spectrum activity, and methods for treating disease using those compns.
IC ICM A61K
CC 1-1 (Pharmacology)
Section cross-reference(s): 63
IT 127779-20-8, Saquinavir 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir **161814-49-9**, Amprenavir 192725-17-0, Lopinavir **206362-00-7**, Uic-94003
RL: DMA (Drug mechanism of action); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(broad spectrum microbial and neoplasmic protein inhibitors)

L22 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:944563 CAPLUS
DOCUMENT NUMBER: 138:11384
TITLE: Methods for determining plasma free drug concentration
INVENTOR(S): Xie, Dong; Cao, Wei; **Erickson, John W.**
PATENT ASSIGNEE(S): Tibotec Pharmaceuticals Ltd., Ire.
SOURCE: Eur. Pat. Appl., 16 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1265073	A2	20021211	EP 2002-77275	20020605
EP 1265073	A3	20031126		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003113748	A1	20030619	US 2002-161613	20020605
US 7087373	B2	20060808		
PRIORITY APPLN. INFO.:			US 2001-295557P P	20010605

ED Entered STN: 13 Dec 2002

AB The present invention relates to methods for isothermal titration calorimetry anal. of the binding affinity of protease inhibitors to plasma proteins.

IC ICM G01N033-94
ICS G01N033-569; G01N033-68

CC 1-1 (Pharmacology)

IT **206361-99-1 206362-00-7 333798-27-9**
RL: ANT (Analyte); ANST (Analytical study)
(methods for determining plasma free drug concentration)

L22 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:79486 CAPLUS

DOCUMENT NUMBER: 136:363282

TITLE: A potent human immunodeficiency virus type 1 protease inhibitor, UIC-94003 (TMC-126), and selection of a novel (A28S) mutation in the protease active site

AUTHOR(S): Yoshimura, Kazuhisa; Kato, Ryohei; Kavlick, Mark F.; Nguyen, Aline; Maroun, Victor; Maeda, Kenji; Hussain, Khaja A.; Ghosh, Arun K.; **Gulnik, Sergei V.**; **Erickson, John W.**; Mitsuya, Hiroaki

CORPORATE SOURCE: Experimental Retrovirology Section, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA

SOURCE: Journal of Virology (2002), 76(3), 1349-1358
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 30 Jan 2002

AB We identified UIC-94003, a nonpeptidic human immunodeficiency virus (HIV) protease inhibitor (PI), containing 3(R),3a(S),6a(R)-bis-tetrahydrofuranyl urethane (bis-THF) and a sulfonamide isostere, which is extremely potent against a wide spectrum of HIV (50% inhibitory concentration, 0.0003 to 0.0005 μM). UIC-94003 was also potent against multi-PI-resistant HIV-1 strains isolated from patients who had no response to any existing antiviral regimens after having received a variety of antiviral agents (50% inhibitory concentration, 0.0005 to 0.0055 μM). Upon selection of HIV-1 in the presence of UIC-94003, mutants carrying a novel active-site mutation, A28S, in the presence of L10F, M46I, I50V, A71V, and N88D appeared. Modeling anal. revealed that the close contact of UIC-94003 with the main chains of the protease active-site amino acids (Asp29 and Asp30) differed from that of other PIs and may be important for its potency and wide-spectrum activity against a variety of drug-resistant HIV-1 variants. Thus, introduction of inhibitor interactions with the main chains of key amino acids and seeking a unique inhibitor-enzyme contact profile should provide a framework for developing novel PIs for treating patients harboring multi-PI-resistant HIV-1.

CC 1-5 (Pharmacology)

IT **206362-00-7**, UIC 94003
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(TMC 126, UIC 94003; potent human immunodeficiency virus type 1 protease inhibitor, UIC-94003 (TMC-126), and selection of a novel (A28S) mutation in protease active site)

IT 30516-87-1, Zidovudine 69655-05-6, Didanosine 127779-20-8, Saquinavir 134678-17-4, 3TC 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir **161814-49-9**, Amprenavir
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potent human immunodeficiency virus type 1 protease inhibitor, UIC-94003 (TMC-126), and selection of a novel (A28S) mutation in protease active site)

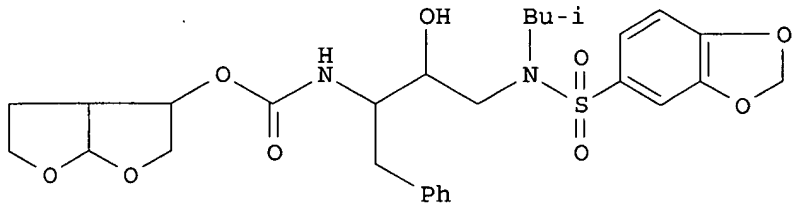
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:265423 CAPLUS
DOCUMENT NUMBER: 134:295811
TITLE: Preparation of hexahydrofuro[2,3-b]furan-3-yl-N-{3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-benzyl-2-hydroxypropyl}carbamate as retroviral protease inhibitor
INVENTOR(S): Wigerinck, Piet Tom Bert Paul; Wang, Guangyang; **Eissenstat, Michael**; **Erickson, John W.**
PATENT ASSIGNEE(S): Tibotec N.V., Belg.; United States Dept. of Health and Human Services
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001025240	A1	20010412	WO 2000-EP9917	20001006
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2386850	AA	20010412	CA 2000-2386850	20001006
AU 2000076638	A5	20010510	AU 2000-76638	20001006
AU 781656	B2	20050602		
BR 2000014602	A	20020611	BR 2000-14602	20001006
EP 1222192	A1	20020717	EP 2000-966144	20001006
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003511383	T2	20030325	JP 2001-528184	20001006
NZ 518580	A	20040130	NZ 2000-518580	20001006
RU 2247123	C2	20050227	RU 2002-111657	20001006
AP 1459	A	20050930	AP 2002-2472	20001006
W: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW				
NO 2002001598	A	20020529	NO 2002-1598	20020404
ZA 2002002655	A	20030704	ZA 2002-2655	20020404
US 6649651	B1	20031118	US 2002-89991	20021223

US 2005261364	A1	20051124	US 2003-606342		20030625
HK 1054746	A1	20051209	HK 2003-107022		20030929
PRIORITY APPLN. INFO.:			US 1999-157850P	P	19991006
			WO 2000-EP9917	W	20001006
			US 2002-89991	A1	20021223

ED Entered STN: 13 Apr 2001
GI



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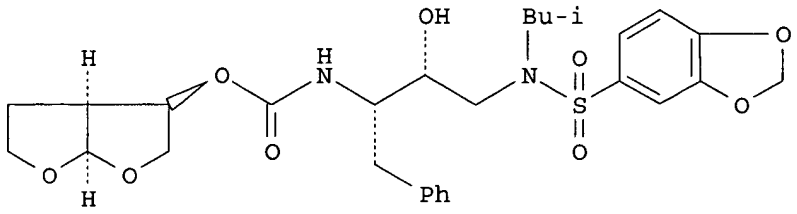


II

AB The present invention relates to novel bis-tetrahydrofuran benzodioxolyl sulfonamide compds. (I) and its stereoisomers which are surprisingly effective protease inhibitors. The invention also relates to pharmaceutical compns., methods of inhibiting retrovirus proteases, in particular multidrug resistant retrovirus proteases, methods of treating or combating infection or disease associated with retrovirus infection in a mammal, and methods of inhibiting viral replication. I and its stereoisomer (II) were tested against 17 HIV-1 strains and showed IC50 of 0.0014 and 0.0008 μM, resp., against HIV-1 LAI strain in MT4 cells.

IC ICM C07D493-04
ICS A61K031-34; A61K031-36; A61P031-12

CC 28-5 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7

IT **333798-26-8P 333798-27-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hexahydrofuro[b]furanyl{[(benzodioxolylsulfonyl)(isobutyl)amino]benzylhydroxypropyl}carbamate as retroviral protease inhibitor)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:819523 CAPLUS
DOCUMENT NUMBER: 132:59135
TITLE: Fitness assay and associated methods, and applications to drug resistance and HIV protease inhibitors and other drugs with reduced resistance
INVENTOR(S): **Erickson, John W.; Gulnik, Sergei V.**
PATENT ASSIGNEE(S): United States of America, Represented by the

Secretary, Department of Health and Human Services, USA
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9967417	A2	19991229	WO 1999-US14119	19990623
WO 9967417	A3	20000928		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2336160	AA	19991229	CA 1999-2336160	19990623
AU 9948280	A1	20000110	AU 1999-48280	19990623
AU 771780	B2	20040401		
EP 1088098	A2	20010404	EP 1999-931861	19990623
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002518063	T2	20020625	JP 2000-556057	19990623
AU 2004200629	A1	20040311	AU 2004-200629	20040218
US 2005158713	A1	20050721	US 2005-30632	20050106

PRIORITY APPLN. INFO.:	US 1998-90393P	P 19980623
	AU 1999-48280	A3 19990623
	WO 1999-US14119	W 19990623
	US 2001-720276	A1 20010307

OTHER SOURCE(S): MARPAT 132:59135
ED Entered STN: 30 Dec 1999
GI For diagram(s), see printed CA Issue.
AB The invention provides an assay for determining the biochem. fitness of a biochem. species in a mutant replicating biol. entity relative to its predecessor. The invention further provides a continuous fluorogenic assay for measuring the anti-HIV protease activity of protease inhibitor. The invention also provides a method of administering a therapeutic compound that reduces the chances of the emergence of drug resistance in therapy. The invention also provides a compound AXQN(R2)CH[(CH2)mR3]CH(R4)CH2N(R5)(WR6) [A = Q1, Q2, Q3, Q4; R1, R2, R3, R5, R6 = H, (substituted and/or heteroatom-bearing) alkyl, alkenyl, alkynyl, or cyclic group; Y, Z = CH2, O, S, SO, SO2, amino, amides, carbamates, ureas, or thiocarbonyl derivs. thereof, optionally substituted with an alkyl, alkenyl, or alkynyl group; n = 1-5; X = bond, (substituted) methylene or ethylene, amino, O, S; Q = C(O), C(S), SO2; m = 0-6; R4 = OH, =O (keto), NH2, alkylamino, including esters, amides, and salts thereof; W = C(O), C(S), S(O), SO2; Optionally, R5 and R6, together with the NW bond comprise a macrocyclic ring], or a pharmaceutically acceptable salt, a prodrug, a composition, or an ester thereof.
IC ICM C12Q001-00
CC 1-1 (Pharmacology)
Section cross-reference(s): 28, 63
IT **206362-00-7P 253265-95-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

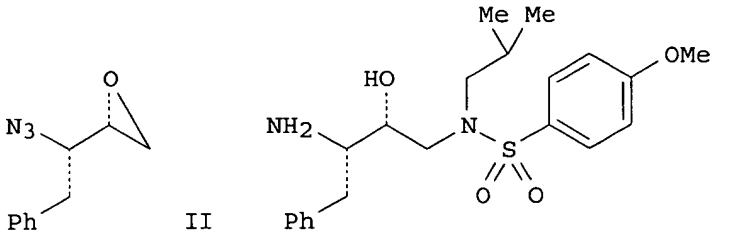
BIOL (Biological study); PREP (Preparation); USES (Uses)
(fitness assay and associated methods, and applications to drug resistance and HIV protease inhibitors and other drugs with reduced resistance)

IT **206361-99-1 206362-01-8 253265-99-5**
253266-00-1 253266-01-2 253266-02-3
253266-03-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fitness assay and associated methods, and applications to drug resistance and HIV protease inhibitors and other drugs with reduced resistance)

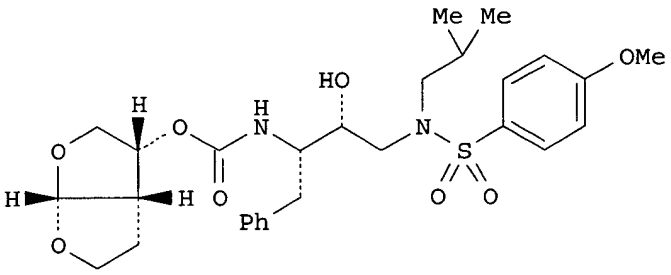
L22 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:819380 CAPLUS
DOCUMENT NUMBER: 132:64254
TITLE: Multidrug-resistant retroviral protease inhibitors and associated methods
INVENTOR(S): **Erickson, John W.; Gulnik, Sergei V.** ; Ghosh, Arun K.; Hussain, Khaja A.
PATENT ASSIGNEE(S): United States Dept. of Health and Human Services, USA; Board of Trustees of the University of Illinois
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9967254	A2	19991229	WO 1999-US14120	19990623
WO 9967254	A3	20000210		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9948281	A1	20000110	AU 1999-48281	19990623
AU 2004200629	A1	20040311	AU 2004-200629	20040218
PRIORITY APPLN. INFO.:			US 1998-90393P P	19980623
			AU 1999-48280 A3	19990623
			WO 1999-US14120 W	19990623

OTHER SOURCE(S): MARPAT 132:64254
ED Entered STN: 30 Dec 1999
GI



II III



IV

AB Nonpeptidic, retroviral protease-inhibiting compds. AZZ1NR2CH[(CH2)mR3]CHR4CH2NR5Z2R6 [I; A = heterocyclyl (structures specified); R2 = H, C1-6 alk(en)yl, C1-6 alkynyl; R3 = (un)substituted (hetero)cycloalkyl, (un)substituted (hetero)aryl; R4 = OH, O, NH2, NHMe; R5 = H, C1-6 alk(en)yl, etc.; R6 = (un)substituted (hetero)cycloalkyl, (un)substituted (hetero)aryl; R5R6 together with NZ2 bond can form a 12-18-membered ring containing ≥1 addnl. heteroatom; Z = bond, CHR10, O, S, NR10, etc.; R10 = (un)substituted alk(en)yl or alkynyl; Z1, Z2 = C(O), S(O), SO2; m = 0-6] or their pharmaceutically acceptable salts, prodrugs, or esters, were prepared Also provided are pharmaceutical compns. for, and therapeutic methods of treating a multidrug-resistant retroviral infection in a mammal. For example, azidoepoxybutane II (4-step preparation from butadiene monooxide and PhMgBr given) was subjected to ring cleavage/amination with Me2CHCH2NH2, the amine amidated with p-MeOC6H4SO2Cl and the azide function of the resulting amide reduced by Pd-catalyzed hydrogenation to give aminosulfonamide III. Transamidation of the latter with (3R,3aS,6aR)-3-hydroxyhexahydrofuro[2,3-b]furyl succinimidyl carbonate (5-step preparation from dihydrofuran and propargyl alc. given) gave a title inhibitor IV which showed nanomolar and sub-nanomolar potency against several multidrug-resistant HIV-1.

IC ICM C07D493-00

CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT **206362-00-7P 253265-95-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of multidrug-resistant retroviral protease inhibitors and associated methods)

IT **206361-99-1 206362-01-8 253265-99-5 253266-00-1 253266-01-2 253266-02-3 253266-03-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of multidrug-resistant retroviral protease inhibitors and associated methods)

L22 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:477765 CAPLUS
DOCUMENT NUMBER: 131:237541
TITLE: JE-2147: a dipeptide protease inhibitor (PI) that potently inhibits multi-PI-resistant HIV-1
AUTHOR(S): Yoshimura, Kazuhisa; Kato, Ryohei; Yusa, Keisuke; Kavlick, Mark F.; Maroun, Victor; Nguyen, Aline; Mimoto, Tsutomu; Ueno, Takamasa; Shintani, Makoto; Falloon, Judith; Masur, Henry; Hayashi, Hideya; **Erickson, John**; Mitsuya, Hiroaki
CORPORATE SOURCE: Experimental Retrovirology Section, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1999), 96(15), 8675-8680
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 03 Aug 1999
AB The authors designed, synthesized, and identified JE-2147, an allophenylnorstatine-containing dipeptide HIV protease inhibitor (PI), which is potent against a wide spectrum of HIV-1, HIV-2, simian immunodeficiency virus, and various clin. HIV-1 strains in vitro. Drug-resistant clin. HIV-1 strains, isolated from seven patients who had failed 9-11 different anti-HIV therapeutics after 32-83 mo, had a variety of drug-resistance-related amino acid substitutions and were highly and invariably resistant to all of the currently available anti-HIV agents. JE-2147 was, however, extremely potent against all such drug-resistant strains, with IC50 values ranging from 13-41 nM (2-fold changes in IC50 compared with that of wild-type HIV-1). The emergence of JE-2147-resistant HIV-1 variants in vitro was substantially delayed compared with that of HIV-1 resistant to another allophenylnorstatine-containing compound, KNI-272, and other related PIs. Structural anal. revealed that the presence of a flexible P2' moiety is important for the potency of JE-2147 toward wild-type and mutant viruses. These data suggest that the use of flexible components may open a new avenue for designing PIs that resist the emergence of PI-resistant HIV-1. Further development of JE-2147 for treating patients harboring multi-PI-resistant HIV-1 is warranted.
CC 1-5 (Pharmacology)
Section cross-reference(s): 75
IT 30516-87-1 69655-05-6, 2',3'-Dideoxyinosine 127779-20-8, Saquinavir 134678-17-4, 3TC 136470-78-5, Abacavir 147318-81-8, KNI-272 150378-17-9, Indinavir 155213-67-5, Ritonavir 159989-64-7, Nelfinavir **161814-49-9**, Amprenavir 186537-85-9, JE 533 186538-00-1, JE 2147 192725-17-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(JE-2147 as dipeptide HIV protease inhibitor that potently inhibits multi-protease inhibitor-resistant HIV-1)
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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